Hypertension

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CHAPTER 9.

SUMMARY AND CONCLUSIONS.

In **chapter 1** the importance of blood pressure as a cardiovascular risk factor and the effects of treatment of hypertension are described. Lowering high blood pressure by antihypertensive treatment has been more successful in the primary prevention of stroke than in the primary prevention of coronary heart disease, the most common complication of hypertension. Several explanations have been put forward to account for this. The treatment duration of most intervention trials may have been too short, concomitant risk factors may not have been adequately controlled, the treatment used may have had negative metabolic effects, and blood pressure may not have been lowered to optimal levels. But another explanation may be that already subclinically present structural and functional cardiovascular changes, may not have been influenced by the treatment used, due to a lack of direct effect of these drugs. On the other hand, blood pressure may not have been controlled optimally during daily life and under conditions such as work, despite adequate office blood pressure reduction.

In **chapter 2** the structural and functional alterations of hypertensive target organs are described more in detail, as well as the role of different methods for early detection of these alterations. Before complications of hypertension become clinically manifest, structural and functional abnormalities of hypertensive target organs can be detected. The brain, the eyes, the kidneys, the arteries and the heart are the major hypertensive target organs. Signs of target organ damage include hypertensive retinopathy, microalbuminuria, decrease of arterial compliance, left ventricular hypertrophy, and impairment of left ventricular diastolic filling. Left ventricular hypertrophy has been shown to have the strongest predictive value for the subsequent development of cardiovascular morbidity and mortality. The presence of left ventricular hypertrophy therefore may serve as a predictor of prognosis in hypertensive subjects. The method most suitable for the early detection of cardiac end organ damage is echocardiography. It is a non-invasive, readily available method,

offering the opportunity to study and quantify both structural and functional characteristics of the left ventricle.

In **chapter 3** alternative methods of blood pressure measurement are discussed more in detail with special reference to their relation with signs of hypertensive end organ damage and with prognosis. All our knowledge about blood pressure as a cardiovascular risk factor is derived from office blood pressure measurements. A reduction of elevated office blood pressure has been proven to improve prognosis in groups of hypertensive subjects. But for the individual patient, office blood pressure is of little prognostic significance. This may be caused by the lack of information given by conventional blood pressure measurements about blood pressure outside the medical environment, during daily life and under special circumstances such as work and physical activity. Compared to office blood pressure, 24-hour ambulatory blood pressure monitoring, self-measurement of blood pressure and exercise blood pressure are better correlated with the presence of target organ damage, especially in the heart. There is some evidence that ambulatory and exercise blood pressure give prognostic information superior to office blood pressure, but definite evidence is still lacking. Therefore, in diagnosing hypertension these methods as yet cannot replace office blood pressure. But 24-hour ambulatory blood pressure monitoring in particular, offers distinct advantages over office blood pressure in the assessment of the efficacy of antihypertensive drugs. Using 24-hour ambulatory blood pressure monitoring, the study size can be reduced, because of better reproducibility compared to office blood pressure. Unlike office blood pressure, ambulatory blood pressure is largely devoid of a placebo effect and can provide evidence for 24 hour therapeutic coverage of a drug. In clinical circumstances such as hypertension resistant to treatment, intermittent symptoms possibly related to blood pressure changes, episodic hypertension, and disparity between clinic and home blood pressure, 24-hour ambulatory blood pressure monitoring gives information which other methods of blood pressure measurement cannot provide.

In **chapter 4** the purpose of the study is given: the assessment of subclinical end organ damage and blood pressure level during daily life and under special circumstances such as physical

activity in subjects, diagnosed as hypertensive according to classical criteria, and the impact of antihypertensive treatment, monitored by conventional blood pressure measurements, on parameters of end organ damage and different measures of blood pressure.

In **chapter 5** the question was addressed whether normalization of elevated office blood pressure in untreated patients in whom hypertension initially had been diagnosed using conventional criteria, implicated the absence of hypertensive disease. A group of 84 subjects identified during a population screening as hypertensive (diastolic blood pressure > 95 mmHg) were followed for a period of 3 months without treatment or advice being given. Seventy subjects became normotensive. Fourteen of these initially hypertensive subjects were compared with all 14 subjects who remained hypertensive and with 14 normotensive subjects, using ambulatory and exercise blood pressure, and both M-mode and Doppler echocardiography. The initial hypertensive and normotensive groups were matched for age and sex with the sustained hypertensive group. Eleven subjects of the initially hypertensive group were re-examined after two years follow-up. The initially hypertensive group did not differ from the sustained hypertensives in 24-hour mean ambulatory and submaximal systolic exercise blood pressure nor in the ratio between early and late diastolic flow velocities (E/A ratio) and in the early diastolic deceleration time (parameters of left ventricular filling). The initial hypertensive group did not differ from the normotensive group in left ventricular mass. After 2 years of observation, the untreated initially hypertensives showed an increase of office diastolic blood pressure to hypertensive values, without change in ambulatory blood pressure. Left ventricular filling abnormalities had become more pronounced while left ventricular mass had not changed. The conclusion of this study was that in subjects, initially diagnosed as hypertensives according to their office blood pressure, and who became normotensive after 3 months follow-up, signs of functional cardiac involvement could be demonstrated similar to those in sustained hypertensives. But opposed to the sustained hypertensives, and despite identical blood pressure load, the initially hypertensives did not have an increased left ventricular mass nor did left ventricular mass increase after 2 years of follow-up, while blood pressure load did not change and

signs of functional cardiac involvement became more prominent, suggesting that the development of left ventricular hypertrophy is a slow process.

In **chapter 6** attention is focused on the effect of treatment, comparing the effects of the angiotensin-converting enzyme inhibitor lisinopril and the beta-blocker metoprolol on blood pressure, especially 24-hour ambulatory and exercise blood pressure, left ventricular mass and exercise tolerance as assessed by maximal oxygen consumption and treadmill time. Furthermore, the relation between treatment induced changes in blood pressure parameters and changes in left ventricular mass was examined. After a treatment period of 12 weeks office blood pressure and daytime ambulatory blood pressure had been reduced to the same extent in both treatment groups (lisinopril n = 10; metoprolol n = 13). Metoprolol showed a more attenuating effect on the excessive systolic blood pressure rise during exercise, although no difference in systolic blood pressure at maximal exercise was found. In both groups, left ventricular mass index did not change during the treatment period. The best correlation between changes in blood pressure parameters and changes in left ventricular mass was found for daytime systolic and diastolic blood pressure in the lisinopril group, but this did not reach statistical significance. A decrease in maximal oxygen consumption was seen in the metoprolol group, but this was not accompanied by a decrease in treadmill time. The conclusion was that lisinopril and metoprolol had the same antihypertensive efficacy in terms of office and ambulatory blood pressure, while both treatment regimens did not induce a decrease in left ventricular mass. Metoprolol influenced exercise blood pressure more favourably than lisinopril, especially at low work loads, without clinical interference with exercise tolerance.

The lack of effect of treatment on left ventricular mass of both lisinopril and metoprolol could be due to the fact that the study population mainly consisted of previously treated hypertensive patients. The next study, described In **chapter 7**, was performed in a group of previously untreated hypertensive subjects, specially focusing on treatment effects on echo Doppler derived parameters of left ventricular diastolic filling, an early sign of cardiac involvement in hypertension. The effects of treatment during 6 months with the angiotensin-converting enzyme inhibitor lisinopril

(n = 20) and the calcium antagonist diltiazem (n = 16) were compared on indexes of left ventricular filling before and after submaximal exercise, left ventricular mass, and office, ambulatory and exercise blood pressure. For assessment of left ventricular diastolic filling, the maximal mitral flow velocities during early left ventricular filling (E-peak) and atrial systole (A-peak) and their ratio (E/A ratio) were used, as assessed by pulsed Doppler echocardiography. The E/A ratio at rest improved significantly in both groups, due to a marked increase of the E-peak and a slight increase of A-peak flow velocity. No intergroup difference was found. The E/A ratio after submaximal exercise did not change significantly in both groups, due to an almost equal increase in E-peak and A-peak flow velocities. No intergroup difference was found between both groups for these parameters. After 6 months of treatment the left ventricular mass index was lower in the lisinopril group, as compared to the diltiazem group. Both treatment regimens showed a similar decrease in office and maximal exercise blood pressure. As compared to diltiazem, lisinopril induced a significantly greater decrease in 24-hours ambulatory blood pressure, which lasted over the entire 24 hours period. In the diltiazem group no decrease in nighttime blood pressure was observed. Changes in diastolic filling parameters were significantly correlated with changes in LV mass index in the lisinopril group and with diastolic daytime ambulatory blood pressure in both groups. The conclusion of this study was that the improvement in left ventricular diastolic filling parameters, observed during treatment with diltiazem LP 300 mg, and comparable to that during treatment with lisinopril 20 mg, must partly be attributed to factors other than blood pressure and left ventricular mass.

Apart from blood pressure, other factors are involved in the increase in left ventricular mass in hypertensive subjects. A decreased arterial compliance, as demonstrated in hypertensive subjects, influences left ventricular mass by increasing systolic blood pressure and subsequently left ventricular wall tension. An increase in left ventricular mass may then serve to normalize wall tension. Arterial compliance is usually assessed by studying pulsatile volume-pressure variations of a segment of an artery. No information is obtained about the non-pulsatile part of a vascular bed. Since this dynamic arterial compliance is blood pressure dependent, changes in dynamic compliance

during antihypertensive treatment do not necessarily reflect changes in functional or structural arterial wall properties. In **chapter 8**, we describe a new method for assessment of static compliance of an upper arm vascular segment. We tested the ability of this method to detect differences between hypertensives and normotensive subjects and changes after intervention, and studied the correlation between changes in compliance parameters and changes in blood pressure and echocardiographic parameters of left ventricular structure and diastolic function, as observed during antihypertensive treatment. The method allows the assessment of the static arterial compliance (dV/dP) of a vascular segment under an occluding cuff around an upper arm segment as a function of mean arterial transmural pressure. Arterial volume can be estimated from the volume shifts under this occluding cuff at varying transmural pressures using a mathematical formula. Volume shifts are derived from changes in electrical impedance during cuff deflation. Mean transmural arterial pressure is assessed by subtracting finger arterial blood pressure from cuff pressure. Thirteen hypertensive subjects were studied before and after 6 months of treatment with the angiotensin-converting enzyme inhibitor lisinopril (n = 6), the calcium antagonist diltiazem (n = 5) or the combination (n = 2). Both classes of drugs have been reported to improve dynamic arterial compliance. Compliance values were compared to those obtained in matched normotensives. Initially, the compliance curve of the hypertensive group was situated to the right of the curve of the normotensive group, characterized by a higher mean arterial transmural pressure at maximum compliance in the hypertensives, indicating a decreased compliance of the arteries of the vascular segment studied. After treatment, the compliance curve of the hypertensives shifted back to the left, characterized by a decrease of mean arterial transmural pressure at maximum compliance. The maximum static arterial compliance of the hypertensive group was significantly lower as compared to the normotensive group and did not change significantly after treatment. Because this maximum arterial compliance is dependent on the total number of open vessels under the cuff, this suggests that in hypertensives less vessels are present in the studied vascular segment. No correlation was found between changes in left ventricular mass or diastolic function and changes in compliance parameters. The

conclusion of this study was that this new method of assessing vascular compliance is able to detect differences between normotensives and hypertensives as well as the effect of treatment. Since the method provides data concerning the compliance of a complete vascular bed over a broad range of arterial transmural pressures, it provides information that is different from that obtained with dynamic compliance measurements.

In **conclusion**: Hypertension is a condition not merely characterized by a high blood pressure. In asymptomatic hypertensives, functional and structural cardiovascular abnormalities can be detected. The presence of certain signs of end organ damage has predictive value for the subsequent occurrence of cardiovascular disease. Some aspects are described in this thesis. Even in subjects, who show a spontaneous normalization of high blood pressure, functional cardiac abnormalities could be demonstrated. In untreated hypertensives, antihypertensive drugs improved functional and structural hypertension induced cardiovascular abnormalities. A difference in effect between representatives of different classes of antihypertensive drugs could be detected on cardiac structure and 24-hour blood pressure despite comparable office blood pressure reduction. From the results of such small scale studies, drugs can be selected on the basis of their ability to improve subclinical end organ damage and to control blood pressure during daily life. Ultimately, large intervention trials should be initiated to study the impact of treatment of hypertension with drugs, selected in this way, on cardiovascular morbidity and mortality.